Nirvanol
(Olanzapine) USP

TABLETS

1. QUALITATIVE AND QUANTITATIVE COMPOSITION
NIRVANOL 5mg TABLETS
Each film coated tablet contains: Olanzapine (USP).....5mg
NIRVANOL 10mg TABLETS
Each film coated tablet contains: Olanzapine (USP).....10mg

2. PHARMACEUTICAL FORM
Coated Tablets for Oral Administration
NIRVANOL 5mg & 10mg tablets are film coated tablets.

3. CLINICAL PARTICULARS
3.1. THERAPEUTIC INDICATIONS
Olanzapine is indicated for the acute and maintenance treatment of schizophrenia and other psychoses where positive symptoms (e.g., delusions, hallucinations, disordered thinking, hostility, and suspiciousness) and/or negative symptoms (e.g., flattened affect, emotional and social withdrawal, poverty of speech) are prominent. Olanzapine also alleviates the secondary affective symptoms commonly associated with schizophrenia and related disorders. Olanzapine is effective in maintaining the clinical improvement during continuing therapy in patients who have shown initial treatment response.

3. 2. POSOLOGY AND METHOD OF ADMINISTRATION
The recommended starting dose for olanzapine is 10mg/day, administered as a single daily dose without regard to meals. Daily dosage may subsequently be adjusted on the basis of individual clinical status within the range of 5-20mg daily. An increase to a dose greater than the routine therapeutic dose of 10mg/day, i.e., to a dose of 15 mg/day or greater, is recommended only after appropriate clinical reassessment.
CHILDREN: Olanzapine has not been studied in subjects under 18 years of age.
ELDERLY PATIENTS: A lower starting dose (5 mg/day) is not routinely indicated but should be considered for those 65 and over when clinical factors warrant. Patients with renal and/or hepatic impairment. A lower starting dose (5 mg) should be considered for such patients in cases of moderate hepatic insufficiency (cirrhosis Child-Pugh Class A or B) the starting dose should be 5mg and only increase with condition. Female compared with male patients: The starting dose and dose range need not be routinely altered for female patients relative to male patients.
NON-SMOKING PATIENTS COMPARED WITH SMOKING PATIENTS: The starting dose and dose range need not be routinely altered for non-smoking patients relative to smoking patients. When more than one factor Is present which might result in slower metabolism (female gender, geriatric age non-smoking status) consideration should be given to decreasing the starting dose. Dose escalation, when indicated, should be conservative in such patients. (See also Section 4.5, interaction with Other Medicaments and Other Forms of interaction and Section 5.2, Pharmacokinetic Properties.)

3.3. CONTRAINDICATIONS
Olanzapine is contraindicated in those patients with a known hypersensitivity to any ingredients of the product. Olanzapine is contraindicated in patients with known risk of arrow-angle glaucoma.

3.4. SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE
CONCOMITANT ILLNESSES: as clinical experience with olazapine in patients with concomitant illness is limited, caution is advised when prescribing for patients with prostatic hypertrophy, or paralytic ileus and related conditions. During anti-psychotic treatment, improvement in the patient's clinical condition may take several days to some weeks. Patients should be closely monitored during this period.
LACTOSE: Olanzapine tablets contain lactose. Transient, asymptomatic elevations of hepatic transaminases, ALI ASI have been seen occasionally, especially in early treatment. Caution should be exercised in patients with elevated ALT and and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs In the event of elevated ALT and/or AST during treatment, follow-up should be organized and dose reduction should be considered. As with other neuroleptic drugs, caution should be exercised in patients with low leukocyte and/or neutrophil counts for any reason, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Thirty-two patients with danzapine related neutropenia or agranulocytosis histories received olanzapine without decreases in baseline neutrophil counts.
NEUROTEPTIC MALIGNANT SYNDROME (NMS): NMS is a potentially life-threatening condition associated with anti-psychotic medication rare cases report as NMS have also been received in association with olanzapine. If a patient develops signs and symptoms indicative of NMS or presents with unexplained high fever without additional clinical manifestations of NMS, all anti-psychotic drugs, including olanzapine must be discontinued. Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur rarely in patients when treated with olanzapine. In most of these cases, history of seizures or risk factors for seizures were reported, tardive Dyskinesia: In comparative studies of one year or less duration, olanzapine was associated with a statistically significant lower incidence of treatment emergent dyskinesia. However the risk of tardive dyskinesia increases with long-term exposure and therefore if signs or symptoms of tardive dyskinesia appear in a patients on olanzapine, a dose reduction or drug discontinuation should be considered. These symptoms can temporarily deteriorate or even arise after discontinuation of treatment.
Given the primary CNS effects of olanzapine, caution should be used when it is taken in combination with other centrally acting drugs and alcohol: As it exhibits in vitro dopamine antagonize, olanzapine may antagonize the effects of direct and indirect dopamine agonists. Potural hypotension was infrequently observed in olanzapine clinical trials. As with other anti-psychotics, it is recommended that blood pressure is measured periodically in patients over 65 years, however, as with other anti-psychotics, caution should be exercised when olanzapine is prescribed with drugs known to increase QTc interval, especially in the elderly. Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare cases during **NIRVANOL** treatment. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

3.5 INTERACTION WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION
Potential for Other Drugs to Affect Olanzapine; Single-doses of antacid (Aluminium magnesium) or cimetidine did not affect the oral bio-availability of olanzapine. However, the concomitant administration of activated charcoal reduced the oral bio-availability of olanzapine by 50 to 60%.
Fluoxetine (60 mg single dose or 60 mg daily for 8 days) causes a mean 16% increase in the maximum concentration of olanzapine and a mean 16% decrease in olanzapine clearance. Therefore dose modification is not routinely recommended. The metabolism of olanzapine may be induced by concomitant smoking (the clearance of olanzapine is 33% lower and the terminal elimination half-life is 21% longer in non-smokes compared to smokes) or carbamzepine therapy (clearance is increased 44% and the increase elimination half-life is reduced by 20% when administered with carbamzepine). Smoking and carbamazepine therapy induce P450-1A2 activity. The pharmacokinetics of theophylline, which is metabolized by P450-1A2 activity on olanzapine pharmacokinetics, has not been studied. Potential for olanzapine to Affect Other Drugs: in clinical trials with single doses of olanzapine, no inhibition of the metabolism of imipramine/desipramine (P450-2D6 or P450-3A4 and P450-2C19) was evident.

3.6 USE DURING PREGNANCY AND LACTATION
PREGNANCY: There are no adequate and well-controlled studies in pregnant women. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with olanzapine. Nevertheless, because human experience is limited, this drug should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.
LACTATION: Olanzapine was excreted in milk of treated rats during lactation. It is not known if olanzapine is excreted in human milk. Patients should be advised not to breast feed an infant if they are taking olanzapine.

3.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINE
Because olanzapine may cause somnolence, patients should be cautioned about operating hazardous machinery, including motor vehicles.

3.8 UNDESIRABLE EFFECTS
FREQUENT (>10%): The only frequently undesirable effects associated with the use of olanzapine in clinical trials were somnolence and weight gain, Weight gain was related to a lower pretreatment body mass index (BMI) and initial starting dose of 15 mg or greater Occasional (1-10%):
Occasional undesirable effects associated with the use of olanzapine in clinical trials included dizziness, increased appetite, peripheral oedema, orthostatic hypotension and mild, transient anticholinergic effects including constipation and dry mouth. Transient, asymptomatic elevations of hepatic transaminases, ALT, AST have been seen occasionally, especially in early treatment (see section 4.4).
In active-controlled studies, olanzapine-treated patients had a lower incidence of parkinsonism, akathisia and dystonia compared with titrated doses of haloperidol in the absence of detailed information on the pre-existing history of individual acute and tardive extra pyramidal movement disorders, it cannot be concluded at present that olanzapine produces less tardive dyskinesia and/or other tardive extra pyramidal syndromes.
RARE (<1%): Photosensitivity reaction and rash were reported rarely. Rare reports

of hepatitis and priapism have been received. Hyperglycemia or exacerbation of pre-existing diabetes has been reported in very rare cases (see also Section 4.4 Special warnings and special precautions for use). Seizures have been reported to occur rarely in patients treated with olanzapine. In most of these cases a history seizures or risk factors for seizures were reported.

OTHER FINDINGS: Plasma prolactin levels were sometimes elevated, but associated clinical manifestation (e.g., gynecomastia, galactorrhea, and breast enlargement) were rare. In most patients, levels returned to normal ranges without cessation of treatment. Rare cases reported as Neuroleptic Malignant Syndrome (NMS) have been received in association with olanzapine (See also Section 4.4).

High creation phosphokinases levels have been observed in rare case haematologic variations such as leucopenia and thrombocytopenia have been occasionally reported.

3.9 OVERDOSE

Experience with olanzapine in over dosage is limited in the patient taking the largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred speech. In the limited number of patients who were evaluated in hospitals, including the patient taking 300 mg, there were no observations indicating an adverse change in laboratory analysis or ECGs. Vital signs were usually within normal limits following overdoses. Based on animal data, the predicted symptoms would reflect an exaggeration of the drugs known pharmacological actions. Symptoms may include somnolence, bysoasis blurred vision, respiratory depression, hypotension and possible extra pyramidal disturbances. There is no specific antidote to olanzapine; therefore, appropriate supportive measures should be initiated. The possibility of multiple drug involvement should be considered.

In case of acute over dosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. The use of activated charcoal for overdose should be considered because the concomitant administration of activated charcoal was shown to reduce the oral bio-availability of olanzapine by 50 to 60%. Gastric lavage (after intubation. If patient is unconscious) may also be considered. Olanzapine is not substantially removed by haemodialysis. Hypotension and circulatory collapse should be treated with appropriate measures such as intervenous fluids and/or sympathomimetic agents such as norepinephrine (do not norepinephrinedepamine or other sympathomimetic agents with beta-agonist activity since beta stimulation may worsen hypotension in the setting of alpha blockade induced by olanzapine). Cardiovascular monitoring should be considered to detect possible arrhythmias. Close medical supervision and monitoring should continue until the patient recovers.

4. PHARMACOLOGICAL PROPERTIES

4.1 PHARMACODYNAMIC PROPERTIES

PHARMACO-THERAPEUTIC GROUP: Olanzapine is an antipsychotic, ATC code N05A H03 (Diazepines and Oxazepiness). Olanzapine is an anti-psychotic agent that demonstrates a broad pharmacologic profile across a number of receptor systems. In preclinical studies, olanzapine exhibited a range of receptor affinities (Ki;<100nM) for serotonin 5 HT 2A/2C 5HT3, 5HT6, dopamine D1, D2, D3, D4, D5; cholinergic muscarinic receptors M_1-M_5; 1 adrenergic; and histamine H1 receptors. Animal behaviour studies with olanzapine indicated 5HT, dompamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater in-vitro affinity for serotonin 5HT2, than dopamine D2 receptors and greater 5HT than D2 activity in vivo, models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A 10)-dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative at anti-psychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other anti-psychotic agents, olanzapine Increases responding in an anxiolytic test. In a single oral dose (10 mg) Positron Emission tomography (PET) study in healthy volunteers, olanzapine produced a higher 5 HT2A than dopamine D2 receptor company in addition, a SPECT imaging study in schizophrenic patients revealed that olanzapine-responsive patients had lower striatal D2 occupancy than some other anti-psychotic and risperidone-responsive patients, while being comparable to danzapine-resposive patients. In two of two placebo and two of three comparative controlled trials with over 2,900 schizophrenic patients presenting with both positive and negative symptoms, olanzapine was associated with statistically significantly greater improvements in negative as well as positive symptoms.

4.2 PHARMACOKINETIC PROPERTIES

Olanzapine is well absorbed after oral administration, reaching peak plasma concentrations within 5 to 8 hours. The absorption is not affected by food Absolute oral bio-availability relative to intravenous administration had not been determined. Olanzapine is metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N glucuronide, which does not pass the Wood brain barrier. Cytochromes, P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites, both exhibited significantly less in vivo pharmacological activities than olanzapine in animal studies. The predominant pharmacologic activity is from the parent olanzapine. After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender in healthy elderly (65 and over) versus non-elderly subjects, the mean elimination half-life was prolonged (51.8 versus 33.8 hrs.). And the clearance was reduced (17.5 versus 18.2 l/hr). The pharmacokinetic variability observed in the elderly is within the range the non-elderly. In 44 patients with schizophrenia >65 years of age. Dosing from 5 to 20 mg/day was not associated with any distinguishing profile of adverse events.

In female versus male subjects the mean elimination half-life was somewhat prolonged (36.7 versus 32.3 hrs) and the clearance was reduced (18.9 versus 27.3 l/hr). However, olanzapine (5-20 mg) demonstrated a comparable safety profile in female (n=467) as in male patients (n=869). In renally impaired patients (creatinine clearance < 10 ml/min) versus healthy subjects, there was no significant difference in mean elimination half-life (37.7 versus 32.4 hr) or drug clearance (21.2 versus olanzapine appeared in urine, principally as metabolites. In smoking subjects with mild hepatic dysfunction, mean elimination half-life (39.3 hr) was prolonged and clearance (18.0 l/hr) was reduced analogous to non-smoking healthy subjects (48.8 hr and 14.1 l/hr, respectively).

In non-smoking versus smoking subjects (male and females) the mean elimination half-life was prolonged (38.6 versus 3.4 hr) and the clearance was reduced (18.6 versus 27 l/hr). The plasma clearance of olanzapine is lower in elderly versus young subjects, in females versus males, and in non-smokers versus smokers however, the magnitude of the impact of age, gender, or smoking on olanzapine clearance and half-life is small in comparison to the overall variability between individuals.

4.3 PRECLINICAL SAFETY DATA ACUTE (SINGLE-DOSE) TOXICITY

Single of oral toxicity in rodents were characteristic or potent neurolepug compounds hypo-activity, coma tremors, clinic convulsions, salivation, and depressed weight gain. The median lethal doses were approximately 210 (mice) and 175 (rats) mg/kg. Dogs tolerated single oral doses up to 10mg/kg without mortality. Clinical signs included sedation, ataxia, tremors, increased heart rate, labored respirator, miosis, and anorexia. In monkeys, single oral doses up to 100 mg/kg resulted in prostration and at higher doses, and, at higher doses, semi-consciousness.

REPEATED-DOSE TOXICITY: In studies up to 3 months duration in mice and up to 1 year in rats and dogs, the predominant effects were CNS depression, anticholinergic effects, and peripheral haematological disorders. Tolerance developed to the CNS depression. Growth parameters were decreased at high doses. Reversible effects consistent with elevated prolactin in rats included decreased weights of ovaries and uterus and morphological changes in vaginal colthelium and in mammary gland.

HAEMOTOLOGIC TOXICITY: Effects on haematologcy parameters were found in each species, including dose-related reductions in circulating leukocytes in mice and non-specific reductions of circulating leukocytes in rats; however, no evidence of bone marrow cytotoxicity was found. Reversible neutropenia, thrombocytopenia, or anaemia developed in a few dogs treated with 8 or 10 mg/kg /day (total olanzapine exposure (AUC) is 12- to 15-fold greater than that of a man given a 12-mg dose), in cytopenic dogs, there were no adverse effects on progenitor and proliferating cells in the bone marrow.

REPRODUCTIVE TOXICITY: Olanzapine had no teratogenic effects. In the offspring of rats given olanzapine, delays in fetal development and transient decreases in offspring activity levels were seen.

MUTAGENICITY: Olanzapine was not mutagenic or clastrogenic.

CARCINOGENICITY: Based on the results of studies in mice and rats, it was concluded that olanzapine is not carcinogenic.

5. SHELF-LIFE: 2 years when stored under appropriate conditions.

6. INSTRUCTIONS

Store below 30°C. Protect from heat, light & moisture. Keep all medicines out of the reach of children. To be sold on the prescription of a registered medical practitioner only.

7. PRESENTATION

NIRVANOL 5mg, 10 mg tablets are available in blister pack of 1x10's.

نروانول ٹیبلیٹس

(اولینزاپین) یوایس پی

ہدایات: **30°** سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ گرمی، روشنی اور نمی سے بچائیں۔

تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔ صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by:
STANDPHARM PAKISTAN (PVT) LTD
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